Central venous catheter infections in outpatients with pulmonary hypertension treated with continuous iloprost

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Abstract: Background: Intravenous prostanoid therapy is one cornerstone of therapy for patients with precapillary pulmonary hypertension (PH). Long-term central venous catheters expose patients to infectious complications. Objectives: We report the incidence of catheter-related infection (CRI) and the spectrum of bacteria for ambulatory PH patients treated with iloprost via non-tunnelled central venous catheters from our Swiss referral centre in Zurich. Methods: Data from 15 PH patients treated with intravenous iloprost between May 2000 and June 2012 were reviewed. Results: We found 11 CRI in 4 cases by two different organisms. Pathogens found were Brevibacterium (55%), Micrococcus luteus (18%), coagulase-negative Staphylococcus (9%) and Staphylococcus aureus (9%), as well as unusual organisms such as Agrobacterium tumefaciens or Delftia tsuruhatensis. The overall CRI rate was 1.28 per 1,000 catheter days, or 0.47 per year. Conclusions: The incidence of CRI using long-term, non-tunnelled central venous catheters in PH patients treated with iloprost is low. Uncommon, rare pathogens causing CRI were found in a substantial number of patients.

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Central Venous Catheter Infections in Outpatients with Pulmonary Hypertension Treated with Continuous Iloprost

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Key Words
Catheter-related infections · Pulmonary hypertension · Prostanoid therapy · Iloprost

Abstract
Background: Intravenous prostanoid therapy is one cornerstone of therapy for patients with pre-capillary pulmonary hypertension (PH). Long-term central venous catheters expose patients to infectious complications. ***Objectives:*** We report the incidence of catheter-related infection (CRI) and the spectrum of bacteria for ambulatory PH patients treated with iloprost via non-tunnelled central venous catheters from our Swiss referral centre in Zurich. ***Methods:*** Data from 15 PH patients treated with intravenous iloprost between May 2000 and June 2012 were reviewed. ***Results:*** We found 11 CRI in 4 cases by two different organisms. Pathogens found were *Brevibacterium* (55%), *Micrococcus luteus* (18%), coagulase-negative *Staphylococcus* (9%) and *Staphylococcus aureus* (9%), as well as unusual organisms such as *Agrobacterium tumefaciens* or *Delftia tsuruhatensis*. The overall CRI rate was 1.28 per 1,000 catheter days, or 0.47 per year. ***Conclusions:*** The incidence of CRI using long-term, non-tunnelled central venous catheters in PH patients treated with iloprost is low. Uncommon, rare pathogens causing CRI were found in a substantial number of patients.

Introduction

Patients with pre-capillary pulmonary hypertension (PH) treated with continuous intravenous prostanoids are at risk for bacteremia, bloodstream infections and sepsis-related death due to long-term indwelling intravenous central catheters. Proper catheter care and patient education are essential in order to prevent infection. Data on catheter-related infection (CRI) from individual specialist centres are limited [1]. The spectrum of bacterial pathogens causing CRI is broad and also differs with the prostanoid used [2–4].

In this observational study we report CRI in PH outpatients treated with continuous intravenous iloprost via non-tunnelled central venous catheters and the spectrum of causative agents. We discuss the role of rare and presumptively apathogenic bacteria cultivated.

Patients and Methods

In our PH referral centre we reviewed the medical history of CRI from all our patients on continuous intravenous iloprost therapy via non-tunnelled central venous catheters from May 2000 to June 2012. All patients gave their written informed consent to have their data registered (Swiss PH-registry, approved by the Swiss federal agency). The diagnosis of PH was established by right heart

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catheterization and was classified according to guidelines [5]. As in other German-speaking centres we used iloprost for severe PH needing an intravenous prostanoid [6]. A central venous catheter was directly placed in the subclavian vein without subcutaneous tunnelling. Patients were intensively educated in catheter care, sterile medication and pump handling. The exit site was always covered by sterile transparent wound dressings that were changed at least every 5 days after application. In any case of potential infection (painful, reddish, swollen insertion sight, or any uncertainty) patients were instructed to seek specialized medical care immediately.

In total we identified 18 PH patients. Three patients were excluded: 2 due to a tunnelled catheter (Hickman and port system) and 1 patient had treatment only during a short pre-mortal intensive care unit stay. The baseline demographics of the included 15 patients are listed in table 1. Follow-up visits after insertion of the central venous catheter were done in our centre. Close contact to each patient gave us access to the full medical history and data of all patients.

We thoroughly reviewed the medical report of the 15 patients for documented or possible CRI. In addition, we checked all microbiological reports for any positive blood culture or catheter tip results in our clinical information system. In cases of uncertainty regarding infection, colonization or contamination, we correlated the microbiological result with the medical history and decided after expert discussion whether the microbiological finding corresponds truly with a CRI according to the definition given by the centre of disease control [7].

Statistical Analysis

Infection rates are reported per 1,000 patient days and annual infection rate. Values are reported as the mean and standard deviation. All microbiologically positive blood culture and catheter tip results are reported and, in case of multiple bacterial growths, all identifications are listed separately.

Table 1. Patient demographics

Patients, n	15
Age (mean ± SD), years	47.27±14.0
Female, n	10 (66.7%)
Diagnoses, n	
IPAH	8
CTEPH	2
Portopulmonary	1
CTD	4
WHO functional class/NYHA, n	
III	6 (40.0%)
IV	9 (60.0%)
6MWD (mean ± SD), m	319±161

IPAH = Idiopathic pulmonary arterial hypertension; CTEPH = chronic thromboembolic PH; Portopulmonary = portopulmonary-associated PAH; CTD = connective tissue disease; 6MWD = 6-min walking distance.

Table 2. Duration of intravenous prostanoid therapy and encountered complications (infections, hospitalisations and death)

Duration of intravenous therapy	
Total, days	8,608
Mean ± SD, days	573.87±498.24
Max./min., days	1,435/75
CRI	
Total	11[1]
Mean per person ± SD	0.73±1.03
Infection rate per 1,000 catheter days	1.28
Annual infection rate ± SD	0.47±0.42
Hospitalisations	10
Ambulatory managed infections	1 (9.1%)
Death related to catheter infection	0

[1] In 4 CRI two etiological organisms could be cultivated.

Results

The total number of catheter days was 8,608 with a range from 75 to 1,435 days. The mean duration was 573.9 ± 498.2 days. During the observed time period we recorded a total of 11 CRI (table 2). In 4 of the CRI two different organisms could be cultured. Nine patients with mean treatment duration of 240 ± 132 days never had a CRI. Patients with CRI had clinical signs of infection at the catheter exit site and/or systemic symptoms [7]. In all cases the catheter was removed and antibiotics therapy initiated. The duration of antibiotic therapy depended on the severity of infection, ranging from single-shot therapy to a treatment duration of maximal 21 days. All the organisms ever cultivated are listed in table 3. In four cultures of the catheter tip only very few colonies were cultivated (3× coagulase-negative staphylococci and 1× *Klebsiella pneumoniae*). In the absence of symptoms and catheter removal for other reasons these results were counted as contamination [8]. Furthermore, some positive blood cultures were found without clinical signs of CRI and counted as contamination *(Micrococcus luteus*, *Moraxella*, alpha-haemolytic streptococci and *Corynebacterium)*.

Coagulase-negative *Staphylococcus* was associated mainly with contamination and found to be responsible for only 1 CRI (9%). Rather surprisingly, we noticed a respectable number of cultivations with organisms that are usually counted as apathogenic in immunocompetent persons: *Brevibacterium* (55%, 6 CRI) and *M. luteus* (18%,

Table 3. Bacterial organisms cultivated in blood cultures or on the catheter tip

Organism	Cultivations n	Contaminations n	CRI positive n
Brevibacterium spp.	6		6 (54.6)
M. luteus	4	2	2 (18.1)
A. tumefaciens	2		2 (18.1)
Coagulase-negative *Staphylococcus*	11	10	1 (9.1)
S. aureus	1		1 (9.1)
M. aurum	1		1 (9.1)
D. tsuruhatensis	1		1 (9.1)
Aeromonas spp.	1		1 (9.1)
Moraxella spp.	2	2	
Enterobacter cloacae	1	1	
Corynebacterium	2	2	
K. pneumoniae	1	1	
Alpha-haemolytic *Streptococcus*	1	1	
Total	34	19	15 (136.36)[1]

Values in parentheses are percentages.
[1] In 4 CRI two etiological organisms could be cultivated.

2 CRI), *Delftia tsuruhatensis*, *Agrobacterium tumefaciens* and *Microbacterium aurum*. The overall CRI rate in our patients was 1.28 per 1,000 catheter days or 0.47 infections per year, with the majority related to usually apathogenic organisms.

Morbidity and Mortality

The 11 CRI led to 10 hospitalizations (91%). We noted no death due to ambulatory acquired CRI.

Discussion

In our cohort of PH patients treated with continuous iloprost via directly inserted non-tunnelled central venous catheters we found a low CRI rate in line with reported rates for PH patients treated with prostanoids via tunnelled central venous catheters. In contrast to other reports, however, the pathogen spectrum in our cohort was shifted towards rare and presumed apathogenic organisms.

The incidence of CRI in patients with various diseases and conditions varies from 0.3 to 9.1 infections per 1,000 catheter days [2, 9–11]. In PH patients, relatively low CRI rates ranging from 0.1 to 1.13 per 1,000 catheter days for tunnelled central venous catheters have been reported [2–4, 12, 13]. Infection rates with treprostinil were found to be higher than with epoprostenol [3]. A single study on continuous intravenous iloprost reports a low CRI rate of 0.41 per 1,000 catheter days [6]. However, incidence rates of different centres vary widely and data on the types and course of infections are rare [3, 13]. Death by catheter-related sepsis is reported in 4 patients (out of 162) in a US [14] registry and 4 (out of 178) in a French registry [15]. The calculated risk of mortality in these studies is not reported.

The CRI rate in our collective treated with iloprost via non-tunnelled catheters is on the upper limit of the reported rates in PH patients, but still low compared to general reports of patients necessitating long-term central venous catheters. Reasons for different CRI rates may be attributed to the patient collective, the insertion technique of the intravenous line, the pharmacological substance given, or the method of data collection. In our PH collective, intravenous therapy with iloprost was used in patients with advanced disease not eligible for transplantation or as a bridge to transplantation according to common practise in German-speaking countries. With 60% of patients being in WHO functional class IV, our patients were severely ill [6, 14–17]. The use of direct subclavian catheters without tunnelling has the advantage of easy and fast placement and removal of catheters in case of therapeutic changes or transplantation. However, a tunnelled approach might be more effective in preventing CRI [18]. Since a higher infection rate with treprostinil compared to epoprostenol was observed, it was speculated that preparation and storage of drugs contribute to an increased incidence of CRI [4]. For long-term iloprost there are no known issues regarding drug handling and CRI. Data collection in our study was done by meticulously reviewing every microbiological result and the entire medical histories. However, the systematic approach and the interval of data collection might influence the published incidence, and the true infection rate might be underestimated in some reports.

An interesting finding of our study is the unexpectedly high number of positive results for *Brevibacterium* spp., causing 6 CRIs in total. The few published cases of clinically relevant infections with this bacterium are mainly reported in immunocompromised or severely ill patients associated with long-term intravenous devices [19–22]. *Brevibacterium* is a Gram-positive coryneform rod. It is part of the normal flora of skin and adjacent structures. Other habitats include raw milk, cheese and animal sources. Since cases of bloodstream infections

with this bacterium as the main etiological pathogen have been reported in the last 2 decades, the pathogenic potential of this bacterium, primarily considered to be apathogenic, should not be underestimated. All our patients who were suffering from CRI with *Brevibacterium* reported symptoms compatible with infection, namely deterioration of general condition, malaise, fever and sometimes chills. The patients were treated successfully with vancomycin and catheter replacement. In some cases antibiotic therapy was escalated with additional moxifloxacin to cover possible lower respiratory tract infection.

It is known that in PH patients treated with intravenous epoprostenol, *Micrococcus* spp. is a common etiological pathogen causing CRI [2, 23, 24]. Similarly, we encountered some *M. luteus* isolates in PH patients treated with iloprost. Reasons for this finding are speculative. Patient- or disease-related factors seem to be more important than drug-related factors. Catheter replacement and antibiotic treatment resolved the CRI successfully.

Furthermore, we found very rare pathogens like *A. tumefaciens (Rhizobium radiobacter)* and *D. tsuruhatensis*. *A. tumefaciens* is an opportunistic pathogen with a low virulence. It preferably infects chronically debilitated and/or immunocompromised patients with intravascular catheters. In a review of 42 combined cases of *Agrobacterium* infections, 100% of patients had underlying malignancy or immunocompromising conditions, and 77% had indwelling intravascular devices. The authors suggest that the pathogens' capacity to adhere to silicone surfaces with extracellular slime contributes to the frequent correlation of infection with indwelling devices [25]. As PH is not thought to lead to immunodeficiency, it remains unclear why these cases came to an infection.

D. tsuruhatensis was first described in 2003 in isolates of activated sludge collected from a domestic wastewater treatment plant in Japan [26]. It has been described as a plant growth-promoting bacterium. In the literature there exists only 1 case report of human infection with this bacterium, occurring in a PH patient on intravenous prostanoid therapy suffering with a CRI [27]. The infection was successfully treated with ciprofloxacin for 21 days and catheter replacement.

Conclusion

In this first report on severely ill PH patients treated with continuous iloprost via non-tunnelled central venous catheters, we found a relatively low incidence of CRI and no associated death. As an interesting finding, we could show that uncommon pathogens, some of which are counted as apathogenic in non-immunocompromised patients, can be found in a substantial number of patients.

Symptoms of CRI can be unspecific and mild in early disease, and therefore clinicians should always be aware of possible CRI in these patients. Since progression may lead to severe illness and eventually death, treatment and replacement of the catheter has to be performed as early as possible.

References

1 Gaine S, Gomberg-Maitland M: Intravenous catheter infections in pulmonary arterial hypertension. Int J Clin Pract 2008;160:3–4.
2 Oudiz RJ, Widlitz A, Beckmann XJ, Camanga D, Alfie J, Brundage BH, Barst RJ: *Micrococcus*-associated central venous catheter infection in patients with pulmonary arterial hypertension. Chest 2004;126:90–94.
3 Bloodstream infections among patients treated with intravenous epoprostenol or intravenous treprostinil for pulmonary arterial hypertension – seven sites, United States, 2003–2006. MMWR Morb Mortal Wkly Rep 2007; 56:170–172.
4 Kallen AJ, Lederman E, Balaji A, Trevino I, Petersen EE, Shoulson R, Saiman L, Horn EM, Gomberg-Maitland M, Barst RJ, Srinivasan A: Bloodstream infections in patients given treatment with intravenous prostanoids. Infect Control Hosp Epidemiol 2008;29:342–349.
5 Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G: Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J 2009;30: 2493–2537.
6 Knudsen L, Schurawlew A, Nickel N, Tiede H, Ghofrani HA, Wilkens H, Ewert R, Halank M, Klose H, Bazner C, Behr J, Hoeper MM: Long-term effects of intravenous iloprost in patients with idiopathic pulmonary arterial hypertension deteriorating on non-parenteral therapy. BMC Pulm Med 2011;11:56.
7 O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, Masur H, McCormick RD, Mermel LA, Pearson ML, Raad II, Randolph A, Weinstein RA: Guidelines for the prevention of intravascular catheter-related infections. MMWR Recomm Rep 2002;51:1–29.
8 Collignon PJ, Munro R: Laboratory diagnosis of intravascular catheter associated sepsis. Eur J Clin Microbiol Infect Dis 1989;8:807–814.
9 van Hoff J, Berg AT, Seashore JH: The effect of right atrial catheters on infectious complications of chemotherapy in children. J Clin Oncol 1990;8:1255–1262.
10 Decker MD, Edwards KM: Central venous catheter infections. Pediatr Clin North Am 1988;35:579–612.
11 Moureau N, Poole S, Murdock MA, Gray SM, Semba CP: Central venous catheters in home infusion care: outcomes analysis in 50,470 patients. J Vasc Interv Radiol 2002;13:1009–1016.

12 Akagi S, Matsubara H, Ogawa A, Kawai Y, Hisamatsu K, Miyaji K, Munemasa M, Fujimoto Y, Kusano KF, Ohe T: Prevention of catheter-related infections using a closed hub system in patients with pulmonary arterial hypertension. Circ J 2007;71:559–564.
13 Ivy DD, Calderbank M, Wagner BD, Dolan S, Nyquist AC, Wade M, Nickels WM, Doran AK: Closed-hub systems with protected connections and the reduction of risk of catheter-related bloodstream infection in pediatric patients receiving intravenous prostanoid therapy for pulmonary hypertension. Infect Control Hosp Epidemiol 2009;30:823–829.
14 McLaughlin VV, Shillington A, Rich S: Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 2002;106:1477–1482.
15 Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Herve P, Rainisio M, Simonneau G: Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J Am Coll Cardiol 2002;40:780–788.
16 Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, Koerner SK, Langleben D, Keller CA, Murali S, Uretsky BF, Clayton LM, Jobsis MM, Blackburn SD, Shortino D, Crow JW: A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296–301.
17 McLaughlin VV, Genthner DE, Panella MM, Rich S: Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med 1998;338:273–277.
18 Doran AK, Ivy DD, Barst RJ, Hill N, Murali S, Benza RL: Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension. Int J Clin Pract Suppl 2008;160:5–9.
19 Ulrich S, Zbinden R, Pagano M, Fischler M, Speich R: Central venous catheter infection with *Brevibacterium* sp. in an immunocompetent woman: case report and review of the literature. Infection 2006;34:103–106.
20 Dass KN, Smith MA, Gill VJ, Goldstein SA, Lucey DR: *Brevibacterium* endocarditis: a first report. Clin Infect Dis 2002;35:e20–e21.
21 Wauters G, Van Bosterhaut B, Avesani V, Cuvelier R, Charlier J, Janssens M, Delmee M: Peritonitis due to *Brevibacterium otitidis* in a patient undergoing continuous ambulatory peritoneal dialysis. J Clin Microbiol 2000;38:4292–4293.
22 Beukinga I, Rodriguez-Villalobos H, Deplano A, Jacobs F, Struelens MJ: Management of long-term catheter-related *Brevibacterium* bacteraemia. Clin Microbiol Infect 2004;10:465–467.
23 Yap RL, Mermel LA: Micrococcus infection in patients receiving epoprostenol by continuous infusion. Eur J Clin Microbiol Infect Dis 2003;22:704–705.
24 Hirata Y, Sata M, Makiuchi Y, Morikane K, Wada A, Okabe N, Tomoike H: Comparative analysis of *Micrococcus luteus* isolates from blood cultures of patients with pulmonary hypertension receiving epoprostenol continuous infusion. J Infect Chemother 2009;15:424–425.
25 Chen CY, Hansen KS, Hansen LK: *Rhizobium radiobacter* as an opportunistic pathogen in central venous catheter-associated bloodstream infection: case report and review. J Hosp Infect 2008;68:203–207.
26 Shigematsu T, Yumihara K, Ueda Y, Numaguchi M, Morimura S, Kida K: *Delftia tsuruhatensis* sp. nov., a terephthalate-assimilating bacterium isolated from activated sludge. Int J Syst Evol Microbiol 2003;53:1479–1483.
27 Preiswerk B, Ullrich S, Speich R, Bloemberg GV, Hombach M: Human infection with *Delftia tsuruhatensis* isolated from a central venous catheter. J Med Microbiol 2011;60:246–248.